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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,911	TING, ALICE Y.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57,81,95,110,111,122 and 146* is/are pending in the application.

4a) Of the above claim(s) *3,5-29,34,36,41-51,57,81,95,111,122 and 146* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,30-33,35,37-40 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I isacknowledged. The traversal is on the ground(s) that there is no serious burden on the examiner to examine the remaining Groups. This is not found persuasive because the search of the different and distinct groups would be a burden. The literature journal search is not coextensive with the foreign and U.S. Patents search.

The requirement is still deemed proper and is therefore made FINAL.

Applicants' election of the following species: azide biotin analog as shown in Fig. 1B; mammalian cell; Seq. ID. 5 for acceptor peptide and Seq. ID. 18 for biotin ligase mutant is also acknowledged. Applicants traverse the species restriction and state that the species elections are made for examination purposes only and that all the species should be considered should the generic claim be found to be allowable.

Applicants state that claims 1, 2,4, 30-33, 35, 37-40 and 52-56 read on the elected inventions and species.

Claims 3, 5-29, 34, 36, 41-51, 57, 81, 95, 111, 122 and 146 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species,

there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

Status of Claims

Claims 1-57, 81, 95, 110-111, 122 and 146 are pending

Claims 3, 5-29, 34, 36, 41-51, 57, 81, 95, 111, 122 and 146 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species.

Claims 58-80, 82-94, 96-109, 112-121, 123-145 and 147-161 have been cancelled.

Claims 1, 2, 4, 30-33, 35, 37-40 and 52-56 are under examination.

Drawings

The drawings are objected to because there is no Seq. ID. Nos. given for the peptide sequences at e.g., Fig. 7. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered

and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 30-33, 35, 37-40 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

The specification at paragraph [0179](U.S. 2004/0209317) describes as an example, mutant BirA that can be applied to the study of PI3-kinase activation in 3T3-L1 adipocytes. These adipocytes display a membrane ruffling response to PDGF and a glucose transport response to insulin, both mediated by PI3-

kinase stimulation. These differing downstream effects may result, according to one hypothesis, from activation of spatially and/or temporally separate pools of PI3-kinase. To test this, a two-tag FRET system is constructed by enzymatically labeling the catalytic and regulatory subunits of PI3-kinase inside cells. Small fluorophores should perturb the system far less than fluorescent proteins such as GFP. This system allows measurement of PI3-kinase activation in real time and at subcellular resolution after insulin or PDGF stimulation. This description relates to studies that should be performed for the claimed method. It is not apparent whether said method has actually been reduced to practice. This generic description is as generic as claimed. The claims do not recite for any structure of the component methods such as fusion protein, biotin analog, and biotin ligase mutant. Each of these components e.g., biotin analog covers a huge scope. The generalities made in the specification would not be a sufficient written description for said genus claims. As applicant states at paragraph [0162]ketone biotin analog (FIG. 1B) is not by itself a biophysical probe, but once conjugated to a protein of interest, can serve as a chemical handle for selective derivatization with hydrazine or alkoxyamine-bearing probes (FIG. 2). This chemistry is specific for the introduced ketone

over other functionalities present on mammalian cell surfaces. (Mahal et al. Science 276:1125-1128, 1997.) Inside a cell, hydrazides must be prevented from coupling to ketone and aldehyde carbonyls of carbohydrates and natural cofactors. At . Paragraph [0176] the disclosure states that the third mutant BirA expression level must be high enough that target proteins will be labeled efficiently. However, overexpression can lead to toxicity. The selection strategy in some instances would favor a stable cell line that expresses the mutant BirA consistently and at moderate levels. Schatz (Biotechnology) at page 1138, col. 2 states that very few protein are biotinylated, only one in E. coli, three in Saccharomyces Cerivisea and four in mammalian cell. This tightly restricted specificity of biotinylation results from the recognition by biotin holoenzyme synthetase of a complex protein domain. These biotinylated domains are highly conserved in a wide variety of species and reside in 80 amino acid regions surrounding the modified lysine. Changes in this domain as far as 33 or more residues from the modified K can abolish biotinylation, presumably because the synthetase recognizes a folded structure. In biotechnological invention one cannot necessarily claim a genus after only describing a limited number of species. There may be unpredictability in the results obtained from species other than those specifically described.

This is evident from the disclosure as stated above and Schatz reference. When there is substantial variation within the genus (e.g., mutant and analogs), one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

Applicants, at the time of filing, are deemed to have not invented species sufficient to constitute the genus by virtue of having disclosed a single species when the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

Claims 1, 2, 4, 30-33, 35, 37-40 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining which target protein can be labeled by a fusion protein with biotin analog, and biotin ligase mutant.

2). The specification failed to provide working examples for the numerous and different type of biotin analog, target protein, biotin ligase mutant and acceptor peptide. The claimed biotin analog or ligase mutant covers a broad scope of mutations e.g., substitution, addition, deletion in the parent ligase, either singly or in combination.

3). The breadth of the claims encompasses a large diversity of biotin analog, ligase, and acceptor peptide and target protein to enable specific labeling of a target protein. See the statement in the disclosure, as stated above.

4). The state of the prior art is such that techniques or methods are specifically applied or adapted for a known or defined structure of a specific acceptor peptide and biotin present in a specific prokaryote or eukaryote.

5). The art is inherently unpredictable because it is not possible to predict which analogs or mutant would reliably predict labeling a specific target protein. See Schatz and applicant's disclosure above.

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art to the numerous undefined variables of the claimed method e.g., microorganism(s) and/or eukaryote(s) containing biotin, acceptor peptide, target protein, analog of biotin and mutant ligase. Applicants do not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 30-33, 35, 37-38 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schatz in view of Oh (5, 168,057) or Huber et al (5,952,185)

Schatz discloses at col. 3, line 35 up to col. 4, line 30 a method for producing biotinylated proteins in vitro and in recombinant host cells. Schatz discloses that biotinylation peptide added to any protein expressed in E. coli with a sufficient time of retention in the cytoplasm to permit BirA to act. If high expression levels of biotinylated protein are desired, then one can readily overexpress the BirA protein at the same time Host cells that lack an endogenous biotin protein ligase (called a biotinylation enzyme) can be transformed with a vector that codes for expression of the birA gene to provide or enhance their ability to biotinylate recombinant proteins. Where, due to the conservation of the recognition domains, the

endogenous biotin-protein ligase of other non-E. coli cell types recognize the novel biotinylation sequences, no such recombinant expression of a biotinylation enzyme is required. One can also perform the biotinylation reaction in vitro using a biotinylation enzyme such as purified BirA, biotin, and biotinylation sequence peptide-tagged proteins, which proteins may be either produced in recombinant host cells or by in vitro translation. One can also use biotin analogues, such as 2-iminobiotin, which has a lower affinity for avidin than biotin and so may be preferred for some applications, in place of biotin, in the method. Schatz does not disclose a biotin analogue as e.g., azide biotin. However, Oh discloses at col. 31, lines 10-23 that commercially available biotin-NHS (5 atoms added to spacer) or biotin-X-NHS (12 atoms added to spacer) may be used. Alternatively, Bis-caproamidobiotin (biotin-X-X-NHS) may be conveniently used where 19 atoms are desired to be added to the spacer. All of these preactivated biotin derivatives readily condense with the omega-amino group of the lysine starting spacer moiety to yield the desired boronic acid-azide biotin (guiding member-reactive member-intended label) tridentate conjugate. The tridentate conjugate shown in FIG. 9 results where biotin-X-X-NHS is employed in the final derivatization step. Huber discloses at col.3, lines 38-41 that

photo-activatable biotin derivatives are known. EP-A-0 155 854 and EP-A-0 187 323 describe azide-substituted phenyls/nitrophenyls which are coupled to biotin via an amine-containing linker. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use in the method of Schatz an azide-biotin analog as taught by either Oh et al or Huber et al. Azide-biotin tags have been known to have conventionally used in the art. One would have been motivated to use an analog since analogs are known in the art to have improved property as compared to the wild or native type compound.

Claims 39, 40 and 52 are free of prior art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw

July 22, 2005